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TO

Examiner Deborah Crouch
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FROM

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COMMENTS

re: SN 09/447,681

Enclosed is the Response filed in the above application on October 18, 2001.

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October 18, 2001 — Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Roth

Serial No.: 09/447,681

Filed: November 23, 1999

For: ADENOVIRUS p53 COMPOSITIONS AND METHODS

Group Art Unit: 1632

Examiner: Crouch, D.

Atty. Dkt. No.: INRP:003–2/GNS

RESPONSE TO OFFICE ACTION
DATED APRIL 18, 2001

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

This paper is submitted in response to the Office Action dated April 18, 2001 for which the three-month date for response was July 18, 2001.

A request for a three-month extension of time to respond is included herewith along with the required fee. This three-month extension will bring the due date to October 18, 2001, which is within the six-month statutory period. Applicant notes that small entity status is now believed to be applicable for this case. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10012299/GNS.

Reconsideration of the application is respectfully requested.

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claim 67 was pending prior to the Office Action dated April 18, 2001. For the Examiner's convenience, the pending claim is shown in the document attached hereto as Appendix A.

B. Double Patenting Rejection

The Action provisionally rejected claim 67 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 29 and 32-34 over copending Application No. 09/668,532 (Attorney docket no. INRP:005USC2).

The substance of this rejection will be addressed at a later date as the rejection is merely *provisional* since the grounds for the rejection is a pending patent application, not an issued patent. Applicant is willing to submit a terminal disclaimer in this case, if appropriate, once the cited application has issued as a patent.

C. The Specification Adequately Describes Claim 67

The Action rejected claim 67 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Action admits there is "general language for a contemplation greater than a retrovirus and a β-actin promoter, " but contends that there is no specific disclosure of another vector construct. The Action then separately considers each passage from the Specification cited by the Applicant and concludes the passages do "not

provide the type of disclosure that would convey to the artisan that applicant possessed the claimed invention at the time of filing." The Action also states that the declaration of Louis Zumstein, Ph.D. was not persuasive. Applicant respectfully traverses this rejection.

Claim 67 recites "An adenovirus vector comprising a wild type p53 gene under the control of a CMV promoter." As argued previously, the written description requirement is whether the "description clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." MPEP 2163.02 (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)). Applicant contends that the cited passages in the Specification accomplish that, noting that the subject matter of the claim "need not be described literally." MPEP 2163.02.

The disclosure at page 8, line 25 to page 9, line 4 provides the indication that embodiments other than a retrovirus are contemplated. Page 14, lines 21-23 describes retroviruses and adenoviruses for use with antisense constructs. This passage, in combination with page 16, lines 5-10 stating that "sense" as well as antisense constructs are contemplated, support an adenoviral construct encoding a gene in the "sense" orientation is included. Page 9, lines 6-12, as the Action admits, indicates that a wild-type p53 operatively linked to a promoter is contemplated, and thus, the combination of page 14, lines 21-23, page 16, lines 5-10, and page 9, lines 6-12 supports an adenovirus under the control of a promoter expressing a p63 gene in the "sense" orientation. Finally, page 15, lines 1-4 indicate that a CMV promoter may be used in place of a β-actin promoter, and even if, as the Examiner contends, these promoters are discussed in the context of retroviral antisense constructs, the passages cited above—page 14, lines 21-23, page 16, lines 5-10, and page 9, lines 6-12—indicate that an adenovirus can replace the

retrovirus and that a p53 sense-encoding construct can replace a p53 anti-sense-encoding construct. Thus, the cited passages provide support for claim 67.

Furthermore, Applicant had previously submitted the declaration of Lou Zumstein, Ph.D. as evidence that a person of ordinary skill in the art would recognize that Applicant had invented what was claimed at the time the application was filed. No *comparable* evidence has been offered by the examiner to rebut the statement from Dr. Zumstein. Applicant is submitting a Substitute Declaration of Louis Zumstein, Ph.D to correct a typographical error in the originally filed Declaration ("page 14, lines 21-23" cited instead of "page 9, lines 21-23"). Based on the arguments presented above, Applicant contends the written description is satisfied for claim 67 and respectfully request this rejection be withdrawn.

D. Claim 67 Is Enabled

Claim 67 was also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, the Action contends that the specification does not provide a source for packaging cell lines for the production of adenoviral vectors that contain the p53 gene in a region of the adenoviral genome essential for replication. It states that while 293 cells were known at the time the application was filed, they could be used only for vectors with a defective E1A region and not for deletions in other areas, such as E2 and E4. Thus, the Action concludes that the breadth of the claim is not enabled. Furthermore, the Action expresses doubt as to the effect of expressing wt-p53 from an adenoviral vector having the E2B gene functional since "[i]t is

known in the art that E2B proteins binds (sic) to the p53 protein and inhibits (sic) its activity." Applicant respectfully traverses this rejection.

As an initial matter, Applicant notes that E1B (not E2B) is an adenoviral protein known to bind p53 and that 293 cells, which were known to those of skill in the art, express both E1A and E1B. Therefore, the doubt expressed in the Action concerning E2B and the effect of expressing wt-p53 from an adenoviral vector at the time the application was filed is unfounded. Applicant respectfully notes that "it is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.05 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). The reasoning provided in this case is not scientifically accurate and thus, Applicant contends that burden of the PTO has not been fulfilled so as to shift the burden of persuasion back to the applicant.

Even if we consider E1B and its binding to p53, the numerous papers that followed the filing of this application confirm that an adenoviral construct containing p53 under the control of the CMV promoter can be made and used to provide expression of p53 to cells. For example, the publications of Liu *et al.*, 1993 and Liu *et al.*, 1994 (Appendices B and C) demonstrate not only the production of an adenovirus that expresses p53 from a CMV promoter, but also the use of such adenovirus in cancer cells to effect p53 expression so as to inhibit those cells.

Moreover, though the Specification does not contain an explicit Example concerning adenoviral construct containing p53, it does teach how to make a retroviral construct containing *ras*. *See* Specification at pages 44-46. "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to

practice it without an undue amount of experimentation." MPEP 2164.02. Applicant contends that it would not require undue experimentation and that none of the arguments in the Action suggest otherwise.

To generate a cell line to complement an adenoviral construct with a deletion in an area other than E1 would not require undue experimentation. At the time the application was filed, a deletion in E3 was also used in adenoviral vectors. *See* Jaffe *et al.* (Appendix D). Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). The additional deletion in E3 shows that while some experimentation might be required to generate deletions in other regions and develop concomitant packaging cell lines to propagate virus, it would not require undue experimentation.

For the reasons discussed above, Applicant contends that the claim do not lack an enabling disclosure and respectfully request this rejection be withdrawn.

E. Claim 67 Is Nonobvious

The Action also rejects claim 67 under 35 U.S.C. § 103 (a) as being unpatentable over Chen *et al.* (Chen), in view of Colicos *et al.* (Colicos) further in view of Pasleau *et al.* (Pasleau). Chen is said to teach retroviral vectors comprising a wild-type human p53 operably linked to the retroviral vector LTR. The Action admits that Chen does not teach an adenoviral vector containing a wild-type p53 gene under the control of a CMV promoter, yet it argues that Colicos teaches infecting cells with an adenovirus containing the *denV* gene under the control of an RSV LTR promoter and that Pasleau teaches a plasmid expression vector encoding bovine growth hormone and its production in transfected rat cells. The Action concludes it would have been

obvious to the ordinary artisan at the time of the instant invention to prepare an adenoviral vector comprising a human wild-type p53 gene operably linked to a CMV promoter to study mammalian gene expression and the transformed phenotype. Motivation is said to be provided by Chen's statement that expression of p53 in Saos cells that lack functional p53 reverts the transformed phenotype, by Colicos's teaching that adenovirus is a suitable vector for the study of mammalian gene expression, and by Pasleau's statement that the CMV promoter gave 3-5 times more expression than the RSV LTR. Applicant respectfully traverses this rejection.

To render claims obvious, the cited references must suggest to those of ordinary skill in the art that they should make the claimed composition. *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). None of the references do this. The Chen article says *nothing* about adenoviral expression vectors or a CMV promoter. Colicos says *nothing* about tumor suppressors or about p53. Instead, it explicitly states, "The results of this work demonstrate that an adenovirus vector can be effectively used to study the expression of **DNA repair genes** in a variety of **untransformed** mammalian cell types." Colicos at page 254 (emphasis added). Colicos not only fails to teach combining its teachings with Chen's teachings, but it suggests against their combination because it urges the study of DNA repair genes, which does not include p53, and it promotes the use of adenoviruses in *untransformed* cell types, which does not include Saos cells. Finally, Pasleau says nothing about adenoviral vectors or p53. Simply because Pasleau may suggest that the CMV promoter can provide higher expression of bovine growth hormone than RSV does not mean that Pasleau suggests or provides the motivation for an adenoviral vector comprising wild type p53 under the control of a CMV promoter. Too much is being read into each of these references.

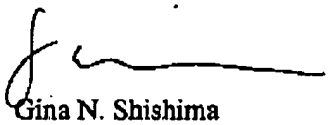
"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The cited references fail to suggest the desirability of the combination. Accordingly, this set of references does not render the claimed invention obvious.

Applicant respectfully requests this rejection be withdrawn.

CONCLUSION

Applicant believes that the present document is a full and complete response to the referenced Official Action. In conclusion, Applicant submits that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable Action is respectfully requested. Should the Examiner have any further questions or comments, or believe that certain clarifications might more readily progress the present application to issuance, a telephone call to the undersigned Applicant's representative at (512) 536-3081 is earnestly solicited.

Respectfully submitted,



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Date: October 18, 2001

APPENDIX A:
PENDING CLAIM

67. An adenovirus vector comprising a wild type p53 gene under the control of a CMV promoter.